

Self-assembly and macromolecular design

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Abstract - The viability of self-assembly as a new concept for the synthesis of novel materials is being vindicated by the creation of increasingly complicated molecular and supramolecular architectures. The extrapolation from alternating donor/acceptor stacks of aromatic rings in the solid state to polycatenanes, polyrotaxanes and double helices in the solution state requires the precise control of molecular recognition processes. This precision is demonstrated by the template-directed synthesis of a wide range of catenanes and rotaxanes. It emerges that, provided the building blocks contain enough molecular information to induce formation of continuously ordered stacks in the crystalline state, then it is possible to exploit this "intelligence" in the self-assembly of exotic macromolecules and polymeric supermolecules in solution.

INTRODUCTION

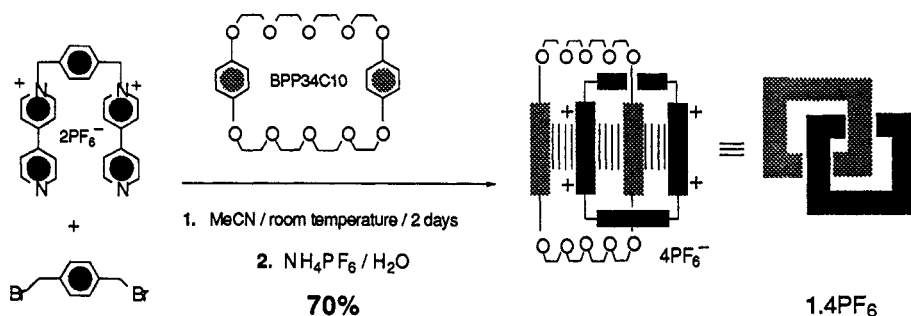
Many of the most impressive discoveries and inventions of this century in molecular science have drawn their inspiration from disciplines outside chemistry, as well as from disciplines who were not chemists. The double helix was a form in art and geometry long before it was revealed in the superstructure¹ of the much venerated DNA molecule. Similarly, knots² and dendrimers³ were contemplated by artists and mathematicians prior to these structures' chemical fruition. Supramolecular chemistry⁴ - the chemistry of the noncovalent bond - is practised and exemplified by biochemical systems. Indeed, the biological world has provided supramolecular chemistry with a gamut of functions and processes which take place, often cooperatively, when complementary molecules interact and react under appropriate conditions. The awe-inspiring efficiency of natural systems alerts us to the fact that the concepts of self-organisation,⁵ self-assembly⁶ and self-replication⁷ are necessary to tame the chemical synthesis of large, well-defined and functioning molecular structures and superstructures. Progress has recently been made towards self-assembling ordered macromolecular architectures reminiscent of tobacco mosaic virus.⁸ In our everyday world, we can marvel at the tremendous physical stability of cables, ropes, knots and chains. This reality poses an intriguing question to the chemist - can we reproduce the features of mechanical entanglement at the molecular level, and if so, what are the consequences in terms of the properties and functions of the materials? Many examples of mechanical entanglement in relatively small synthetic chemical systems have already been demonstrated. Catenanes and rotaxanes were first isolated in meagre amounts⁹ using statistical synthetic approaches. Self-assembly processes⁶ have revolutionised the construction of these interlocked molecules,¹⁰ and have made possible the preparation of the knots¹¹ and helices¹² by template-directed methods. The formation of these entangled molecules and supermolecules has now been achieved with remarkable efficiency, even although the precise nature of the self-assembly mechanisms has yet to be expounded fully. Few examples, however, of the related polymeric systems of macromolecular dimensions have been reported. Polyrotaxanes¹³ have been described, but their structures are rather illly defined. The next generation of macromolecules will exploit the synthetic methodology of catenane, rotaxane, knot and helix formation for controlled polymer self-assembly. They will be made just as much for their functional, as for their structural, properties.

FROM MOLECULAR RECOGNITION TO SELF-ASSEMBLY

To create ordered macromolecular structures in a controlled manner, chemists must devise and develop clever approaches which manipulate intermolecular and intramolecular forces as well as covalent bond-forming reactions. Self-assembly is the ideal synthetic paradigm to fit these requirements.¹⁰ Molecular recognition precedents provide supramolecular chemists targeting self-assembly with the polymer chemists' equivalent of monomeric building blocks. Efficient self-assembly processes will originate from the utilisation of the increasingly inexhaustible supply of knowledge that is being amassed concerning host-guest binding interactions. Creative thinking will result in the application of this knowledge and experience to the design of macromolecular systems whose self-synthesis will be more and more efficient on a relatively short timescale.

Strict self-assembly⁶ requires the construction of molecular compounds prior to the organising event. Such an approach demands careful programming (design) of the structural components, such that they contain all the information necessary for the spontaneous formation of the target superstructure. The self-assembly of metal helicates from transition metal ions and strands containing 2,2'-bipyridine units is an excellent example^{11, 14} of this methodology at work. The self-assembly of the helicates derives its efficiency from the established tetrahedral and octahedral¹⁴ coordination of the bipyridine unit to copper (I) and nickel (I) ions, respectively.

Scheme 1



Template-directed self-assembly of a [2]catenane

The self-assembling systems discussed here rely on the noncovalent bonding interactions between molecular components containing π -electron rich and π -electron deficient aromatic rings.¹⁰ The high binding constants of bisparaphenylene-34-crown-10 (BPP34C10) with paraquat¹⁵ and of the cyclobis(paraquat-*p*-phenylene) with guests containing π -electron rich aromatic rings¹⁶ suggested what proved to be the extremely efficient template-directed self-assembly¹⁷ of the [2]catenane 1.4PF₆, shown in Scheme 1. The Scheme introduces the cartoons which will be used as an aid to discussing the applications of our methodology to the self-assembly of macromolecules. The mechanism of self-assembling the [2]catenane and, by now, many derivative structures¹⁰ is reminiscent of the self-assembly of viruses, such as bacteriophage T4, where covalent modifications are alternated with noncovalent association until the final entity is reached. This mechanism is tantamount to self-assembly with intermittent processing - a subject we shall return to later. The solid-state structure of 1.4PF₆, determined by X-ray crystallography, shows that, within each molecule, there is parallel stacking of the π -electron deficient paraquat residues and the π -electron rich hydroquinol rings. Also in evidence are hydrogen bonds between the oxygen atoms at the centre of the polyether spacers in BPP34C10 and the hydrogen

atoms attached to the carbon atoms adjacent to the quaternary nitrogen atoms in the tetracationic cyclophane. The π - π stacking extends beyond each [2]catenane molecule into infinite columns of alternating π -electron donor and π -electron acceptor units that stretch along an entire crystallographic axis.

The order that prevails in the "polymer-like" stacks of the [2]catenane 1.4PF₆ in the solid state is mirrored in the crystal structures^{18, 19} of the complex of a crown ether containing two 1,5-dioxy-naphthalene residues with paraquat and of a pseudorotaxane^a self-assembled from an oligomer containing three π -electron rich hydroquinol rings and cyclobis(paraquat-*p*-phenylene). Since the building blocks contain apparently sufficient molecular information to induce formation of continuously ordered stacks in their crystals, then, under optimum conditions, it should be possible to exploit this "intelligence" in the self-assembly of exotic macromolecules and polymeric supermolecules in solution.

TOWARDS MACROMOLECULES CONTAINING ENTANGLED COMPONENTS

The notion of synthesising molecules which incorporate the aspect of mechanical entanglement within their component superstructures is extremely appealing. The feature of mechanical entanglement involving molecular strands may have practical implications for the physical and chemical properties of the derived materials. Attention has already been drawn¹³ to the many structural possibilities comprising polyrotaxanes. Self-assembly is an ideal paradigm for the controlled creation of such structures. The aspect of physical restraint between the components in the materials may not even be necessary, provided that good molecular recognition processes prevail. Self-assembly could be used to advantage for the preparation of pseudopolyrotaxanes,^a polypseudorotaxanes^a and polyhelices.

There is a logical conceptual progression that can be traced from donor-acceptor stacks, through complexes of macrocycles with complementary hosts to the stacked [2]catenanes (Fig. 1). This sequence requires no more than formally connecting the termini of the donors or of the acceptors, respectively. If we vary the siting of the linkers, then we can envisage many intriguing new superstructures that relate back to the same continuous stack. For example, we can foresee pseudopolyrotaxanes based on either 'dark-light' or 'light-dark' logic, or, by carrying out further variations on this theme, double helices. As we progress from donor-acceptor stacks to stacked [2]catenanes, we increase the degree of mechanical involvement as well as augment the molecular information in the superstructure. This trend means that the molecular components must contain more information before the self-assembly event. In other words, the molecular components require increasingly refined programming with respect to the information that they contain. In the case of the [2]catenane, the preorganised crown ether ring must be prepared prior to catenation.

On formally rearranging the stacked [2]catenanes into a double helix, the two components become completely free of mechanical interlocking, but retain mechanical entanglement, *i.e.* they can be separated without the breaking of a covalent bond. At the same time, the information content of the

^a Pseudorotaxanes are the complexes formed between a linear molecule and one or more macrocycles.

They are analogous to rotaxanes, with the exception that the macrocyclic components are not imprisoned on the linear component by stoppers. Pseudopolyrotaxanes are polymeric structures comprised of a linear macromolecule which incorporates numerous macrocycles along its length.

Polypseudorotaxanes are a covalently linked array of pseudorotaxanes, where the macrocycles are not confined on the polymer backbone, but rather on to strands emanating from the polymer backbone.

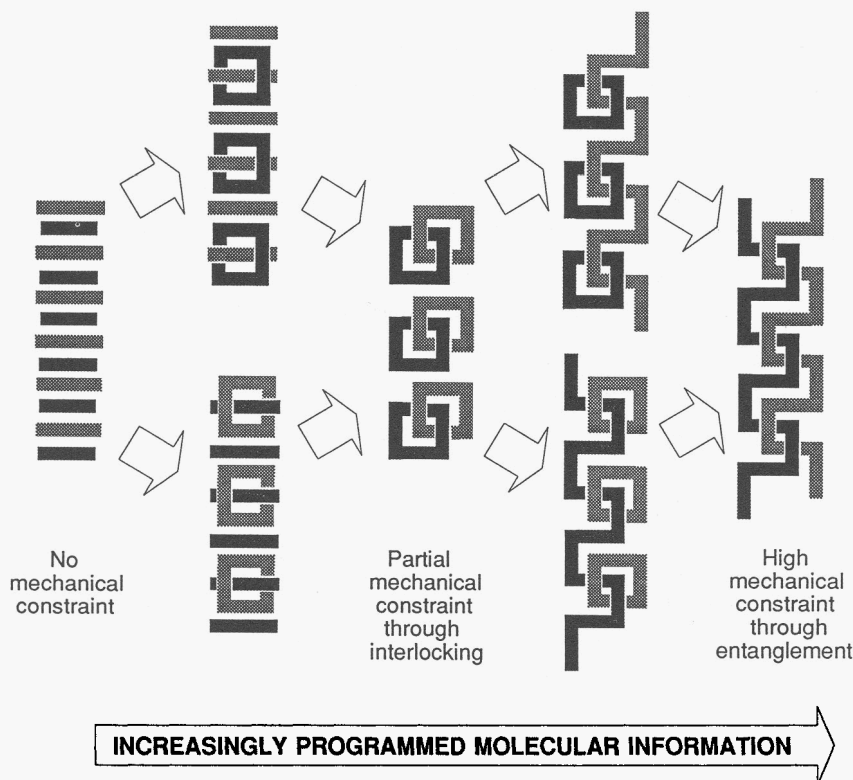


Fig. 1. From donor-acceptor stacks in the solid state through stacked [2]catenanes to a double helix

system has to be increased by virtue of the greater size, and therefore information content, of the assembly. Consequently, as in the case of Lehn's double and triple helicates,^{11, 14} precise pre-programming is necessary if strict self-assembly is to be adhered to in the event. However, provided the components are well designed, iterative self-assembly processes can be utilised for more ready and rapid creation of entangled double helices.

Self-assembled pseudopolyrotaxanes²⁰ have already been realised by threading cyclobis(paraquat-*p*-phenylene) units on to prefabricated polymeric threads incorporating π -electron rich hydroquinol units. We have also made inroads into the realm of double helices²¹ constructed from molecular strands interspersed with appropriate donor-acceptor building blocks. Success here has been more difficult to come by than in the preparation of the catenanes and rotaxanes, owing to the decreased preorganisation of the binding sites and the lack of sufficient cooperativity between the strands that have been designed and synthesised to the present.

The information that is contained within a pseudopolyrotaxane superstructure can be trapped for all time in a molecular structure by the attachment of bulky groups - stoppers - to the termini of the linear thread component, thus forming a polyrotaxane. The self-assembly of rotaxanes can be achieved by one of three general methods (Fig. 2).

Threading²² requires binding of macrocycles to the recognition sites in a linear thread, followed by covalent fixing of stoppers to either end of the thread. Recently, we described²³ the "intelligent" threaded self-assembly of a [2]rotaxane (Fig. 3). It may prove to be the prototype for a series of larger well-defined structures. Four pre-programmed buiding blocks combine to form a [2]rotaxane which

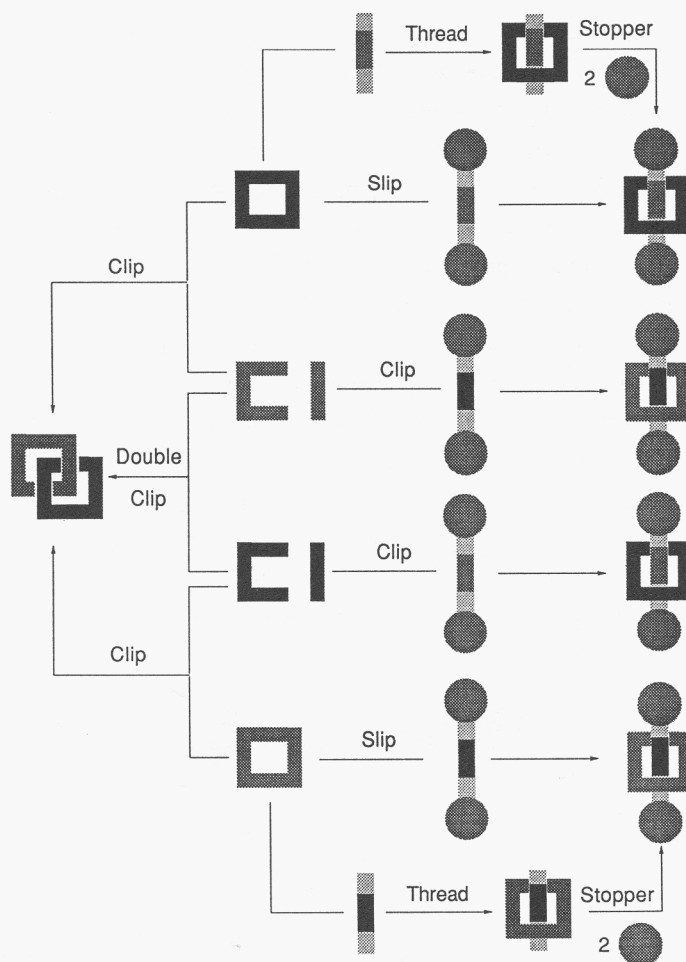


Fig. 2. Self-assembly routes to [2]catenanes and [2]rotaxanes

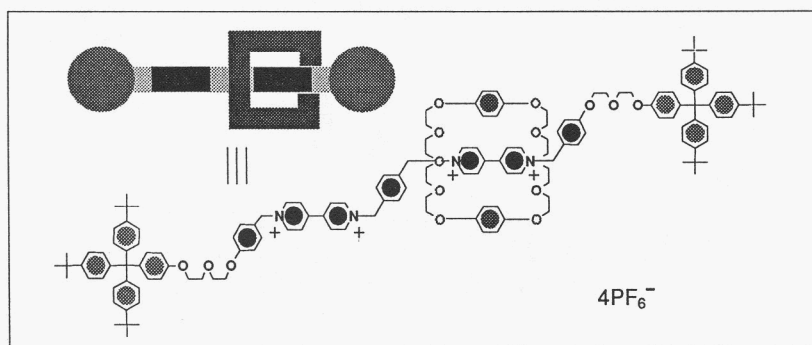
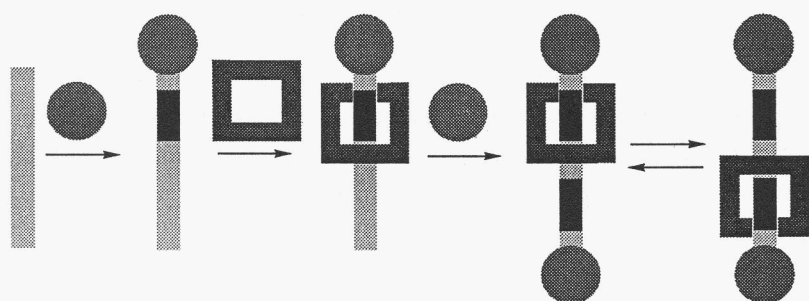


Fig. 3. "Intelligent" self-assembly of a [2]rotaxane

contains two binding sites, and which is, therefore, a molecular shuttle.²⁴ In principle, for every n paraquat units in the thread, there will be $n-1$ BPP34C10 rings incorporated between the two stoppers. The "intelligence" of the self-assembly process arises from the relatively weak binding of the monosubstituted cationic 4,4'-bipyridine unit when compared with the corresponding disubstituted dicationic unit. Clipping²⁵ and slipping²⁶ both require the prefabrication of a dumbbell-shaped molecule by a traditional synthetic approach. The macrocyclic component(s) can then be clipped on to the thread by self-assembling the constituent parts of the macrocycle around the templating portions of the dumbbell. Alternatively, by fine-tuning the size of the stopper, the macrocycles can be slipped on to the dumbbell at elevated temperatures in solution. Cooling down the solutions affords the thermodynamically stable rotaxanes after chromatography. This approach was investigated years ago²⁷ in the absence of an efficient template on the dumbbell, and, not unexpectedly, very low yields of rotaxanes were obtained. We have recently demonstrated the high-yielding slippage²⁶ of BPP34C10 on to dumbbells incorporating paraquat residues as recognition sites. The slippage was achieved by replacement of a *t*-butyl group on the stopper with successively smaller groups, *i.e.* isopropyl, ethyl and methyl. In this way, we have obtained the "unnatural" product from the "intelligent" [2]rotaxane self-assembly process, that is the [3]rotaxane (Fig. 4), where there is a BPP34C10 component present for each recognition site in the dumbbell.

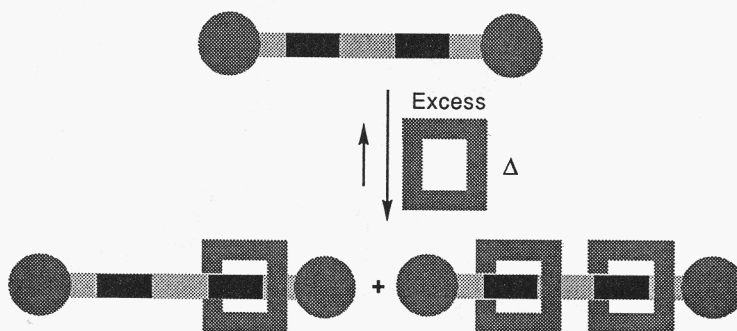


Fig. 4. Self-assembly of a [2]rotaxane and [3]rotaxane by slippage

The slippage method can, in principle, be used for the self-assembly of polyrotaxanes (Fig. 5) where every recognition site in a dumbbell is bound by one macrocycle. Alternatively, by undernourishing the dumbbell with macrocycles, partial coverage of the recognition sites can be achieved. Thus, we have discovered a route to the tuning of polymer properties and functions that relies upon a ridiculously simple self-assembly process.

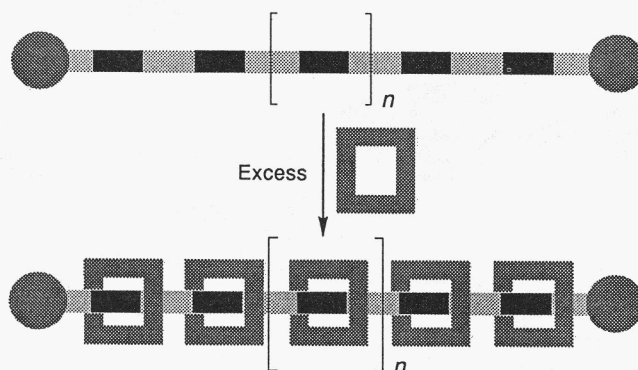


Fig. 5. The application of slippage to the controlled creation of polyrotaxanes

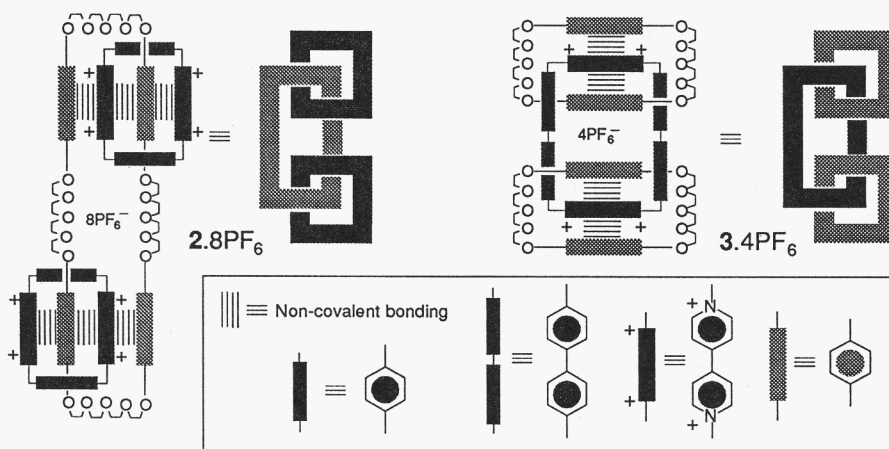


Fig. 6. Two self-assembled [3]catenanes - a way forward to polycatenanes?

Polycatenanes are perhaps one of the most appealing and challenging macromolecular structures whose synthesis remains as yet untamed by polymer scientists. One can marvel at the tremendous physical strength of chains to which anchors are attached, and ponder on the properties that structures of this kind on the molecular scale might display to the world at large. The increased number of interactions that are required for the chain construction of a polycatenane means that much more recognition information is necessary than that needed for the formation of polyrotaxanes, or even helices. We can approach this challenge by increasing the preorganisation of the components used in the self-assembly process. We have already characterised [3]catenanes $2.8PF_6$ and $3.4PF_6$ (Fig. 6), from which one could conceive of planning a route to polycatenanes. In the knowledge that a crown ether interspersed symmetrically with four hydroquinol rings (TPP68C20) can form a [3]catenane²⁸ with two small cyclobis(paraquat-*p*-phenylene) cyclophanes at ultra-high pressure, and that a cyclobis(paraquat-1,1'-[4,4'-biphenylene]) cyclophane forms a [3]catenane²⁹ with two BPP34C10 crown ethers incorporated, we might hope that, by combining the components used to construct the extended cyclophane with TPP68C20, we should produce higher order catenanes, or even polycatenanes (Fig. 7). Alas, no catenated materials were isolated after numerous attempts. The reduced preorganisation of the TPP68C20, when compared with that of BPP34C10, clearly means that catenations involving the larger crown ether are not nearly as efficient as those involving the smaller crown ether. This recipe amounts to insufficient molecular information.

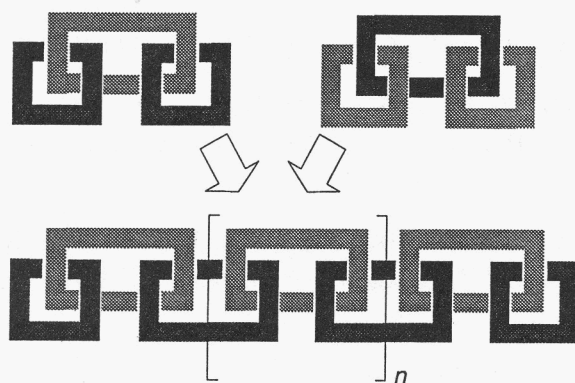


Fig. 7. The conceptual journey from $2.8PF_6$ and $3.4PF_6$ to a polycatenane

Recently, however, we managed to self-assemble a [4]catenane³⁰ by using a crown ether - a 51-crown-15 - incorporating three hydroquinol rings, which contains the necessary molecular information to react with the components of the cyclobis(paraquat-1,1'-[4,4'-biphenylene]) cyclophane. Currently, we are concentrating our efforts on increasing the efficiency still further in order to address the appealing challenge of polycatenanes - not to mention the olympic opportunity provided by a [5]catenane!

Aside from the genuine polycatenane structure, one can envisage numerous types of polymeric structures containing functionalised catenane monomeric and oligomeric units, which might be connected together forming a polymeric strand with appended catenanes. The recent self-assembly of a bis[2]catenane³¹ is an example of the way in which catenanes can be joined together in linear arrays. The range of possible polymeric structures within our grasp is limited only by our imaginations³² in geometrical and topological domains.

REFLECTIONS AND ASPIRATIONS

Self-assembly is a viable synthetic paradigm for the construction of large, well-defined structures and superstructures. Nature shows us that! The power to self-assemble large ordered wholly-synthetic structures and superstructures packed with molecular information is becoming available at a considerable rate of knots! The challenge for the 21st century is to find out how to make use of this information.

Acknowledgements

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